Title

The network structure of ICD-11 Disorders Specifically Associated with Stress: Adjustment Disorder, Prolonged Grief Disorder, Posttraumatic Stress Disorder (PTSD) and Complex PTSD

Brief Title

The network structure of ICD-11 Disorders Specifically Associated with Stress

Authors

*Thanos Karatzias PhD[1,2], Matthias Knefel, PhD[3], Andreas Maercker, MD[4], Marylene Cloitre, PhD[5,6], Geoffrey Reed, PhD[7], Richard Bryant, PhD[8], Menachem Ben-Ezra, PhD[9], Evaldas Kazlauskas, PhD[10], Sally Jowett, DClinPsych[11], Mark Shevlin, PhD[12], Philip Hyland, PhD[13]

Affiliations

[1]School of Health & Social Care, Edinburgh Napier University, Edinburgh, Scotland
[2]Rivers Centre for Traumatic Stress, NHS Lothian, Edinburgh, Scotland
[3]Faculty of Psychology, University of Vienna, Vienna, Austria
[4]Division of Psychopathology, Department of Psychology, University of Zurich, Zurich, Switzerland
[5]National Center for PTSD, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA
[6]Department of Psychiatry and Behavioral Sciences, Stanford University, California, USA
[7]Department of Psychiatry, Columbia University, New York, NY, USA
[8]School of Psychology, University of New South Wales, Sydney, Australia
[9]School of Social Work, Ariel University, Ariel, Israel
[10]Center for Psychotraumatology, Institute of Psychology, Vilnius University, Vilnius, Lithuania
[11]NHS Education for Scotland, NHS Lothian, Edinburgh, Scotland
[12]School of Psychology, Ulster University, Coleraine, UK
[13]Department of Psychology, Maynooth University, Kildare, Ireland

***Corresponding author:** Prof Thanos Karatzias, School of Health & Social Care, Edinburgh Napier University, Edinburgh, EH11 4BN, Scotland, UK
email: t.karatzias@napier.ac.uk, tel. 0044 131 455 5345

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Abstract

Introduction: The ICD-11 includes a new grouping for "Disorders Specifically Associated with Stress" that contains revised descriptions of Posttraumatic Stress Disorder (PTSD) and Adjustment Disorder (AjD) and new diagnoses in the form of Complex PTSD (CPTSD) and Prolonged Grief Disorder (PGD). These disorders are similar in that they each require a life event for the diagnosis, however they have not yet been assessed together for validity within the same sample. We set out to test the distinctiveness of the four main ICD-11 stress disorders using a network analysis approach.

Methods: Population-based, cross-sectional design. A nationally representative sample of adults from the Republic of Ireland aged 18 years and older (N = 1,020) completed standardised measures of PTSD, CPTSD, AjD and PGD. A network analysis was conducted at symptom level. Outcomes measures included the International Trauma Questionnaire, the Inventory of Complicated Grief, and the International Adjustment Disorder Questionnaire.

Results: Consistent with the taxonomic structure of the ICD-11, our results showed that although the four conditions clustered independently at disorder level, the specific symptoms of PTSD, CPTSD, PGD, and AjD clustered together very strongly, but more strongly than with symptoms of the other disorders. The majority (61%) of the variation in each symptom could be explained by its neighbouring symptoms. The strongest trans-diagnostically connecting symptom was "startle response".

Discussion / Conclusion: Mental health professionals caring for people who have experienced a range of stressors and traumatic life events can be confident in diagnosing these conditions that have clear diagnostic boundaries. Interventions addressing stress-associated disorders should be based on diagnostic assessment to ensure close fit between symptoms and treatment.

Introduction

Stressful and traumatic life events are common and are associated with several psychiatric diagnoses [1,2]. The ICD-11 [3] includes a new grouping for "Disorders Specifically Associated with Stress" that contains revised descriptions of Posttraumatic Stress Disorder (PTSD: PB40) and Adjustment Disorder (AjD: PB43), and new diagnoses in the form of Complex PTSD (CPTSD: PB41) and Prolonged Grief Disorder (PGD: PB42). These disorders are similar in that they each require the occurrence of a life event for the consideration of a diagnosis. In this study we examine the network structure of PTSD, CPTSD, PGD, and AjD to evaluate the symptom connections within and across diagnostic boundaries. It is expected that there will be strong connections within diagnoses as well as between some symptoms which might identify as transdiagnostic symptoms. A brief description of this disorders is provided as follows.

PTSD and CPTSD are disorders that can occur following exposure to (a) traumatic event(s), which is defined as any extremely threatening or horrific event [4]. PTSD includes three symptom clusters of Re-experiencing in the here and now, Avoidance of Traumatic Reminders, and Sense of Current Threat, while CPTSD includes six symptom clusters: three are shared with PTSD along with Affective Dysregulation, Negative Self-Concept, and Disturbed Relationships the latter of which are collectively termed 'Disturbances in Self-Organization' (DSO) [5]. PGD may occur following the death of a person close to the bereaved and is characterised by persistent and pervasive longing or preoccupation for the deceased. Importantly, the grief response needs to have persisted for an atypically long time and exceed sociocultural norms. Finally, AjD can occur following a psychosocial stressor or multiple stressors (e.g., job loss, divorce), and is characterized by preoccupation with the stressor (e.g., excessive worrying) and failure to adapt to the stressor (e.g., inability to regain emotional equanimity) [6]. Studies have shown that these disorders, and the events that may

94 precipitate them, are frequently observed in the general population [5-7], and are very
95 common in clinical samples [8,9].
96 Self-report measures for each of these disorders have been developed (and are freely
97 available in multiple translations from https://www.traumameasuresglobal.com/) and have
98 been widely used across different nations and different cohorts exposed to different kinds of
99 stressors. Based on data derived from these measures, there is considerable evidence to
100 support the construct validity of PTSD and CPTSD [9], and less but growing evidence to
101 support the construct validity of AjD and PGD [6]. Evidence of validity, including the
102 discriminant validity of each disorder, has mainly been derived from studies using latent
103 variable modelling techniques, however, a growing number of studies have used the
104 conceptually distinct approach of network analysis [10]. These studies have predominantly
105 focused on PTSD and CPTSD and have found a network of symptom connections that
106 correspond to the symptom clustering as outlined in ICD-11 [11-13].
107 While there is evidence to support the construct validity of each of these stress-related
108 disorders, no study has yet evaluated these four disorders together in the same sample. Given
109 that PTSD, CPTSD, PGD, and AjD are conceptually similar in that they are all persistent
110 maladaptive reactions to life stressors, and that they likely share similar aetiological factors
111 such as memory alterations [14], it is highly probable that the symptoms reflecting these
112 disorders interact in important ways. Network analysis is an ideal method to explore
113 symptom connections within and across diagnostic boundaries. Network analysis provides a
114 visual representation of symptom interaction within and between disorders and can illustrate
115 which symptoms are more central than others, which, if prioritised in therapy, this will enable
116 rapid response to treatment. This analytical strategy is rooted in the network approach to
117 psychopathology [15] that specifies mental disorders as networks of directly and indirectly
118 interacting symptoms. Opposing the traditional latent variable view of psychopathology, this

approach does not assume the presence of a latent disorder that explains symptom covariation. Rather, symptoms are supposed to directly influence one another, within but also across disorder boundaries, explaining the presence of comorbidity. This approach seems to be of particular relevance for ICD-11's Disorders Specifically Associated with Stress, as these disorders share similar features but also should form distinguishable disorders. Investigating symptom covariance within and across disorder boundaries may add to a network psychometric validation of the disorders at stake [16].

In this study, we set out to examine the network structure of PTSD, CPTSD, PGD, and AjD. Assuming the ICD-11's diagnostic classification has conceptual integrity, we hypothesised the existence of a network of positively related symptoms where the symptoms within a given disorder clustered more strongly to one another than to symptoms of other disorders. However, recognising that diagnostic boundaries are rarely perfect demarcations between conditions[17] and following the network approach, we hypothesised that some symptoms would evidence trans-diagnostic features. We aimed to identify which, if any, symptoms act as 'bridges' between the disorders.

Methods

Participants

This study utilized data from a nationally representative sample of adults aged 18 years and older from the Republic of Ireland (N = 1,020). Participants were drawn from existing online, nationally representative panels. Participants in this sample were selected using quota sampling procedures to construct a dataset that represented the Irish adult population based on sex, age, and geographical distribution. The data were collected by an Ireland based survey company, Qualtrics, and participants were remunerated by Qualtrics for their time. Participants were contacted via email, text, or in-app notification, and to avoid selection bias, were provided with minimal information about the study at this first contact. If participants

followed the provided link to the Qualtrics platform to complete the survey, they were provided with a detailed information sheet about the nature of the study and asked to provide their consent prior to participating. The data were collected in February 2019, and the median time of completion of the survey was 22 minutes.

All participants indicated exposure to at least one stressful life event; 87.7% (n = 895) indicated exposure to at least one traumatic event; and 81.4% (n = 830) indicated a bereavement (details on the measurement of these events in outlined in the next section). In total, 73.5% (n = 750) of individuals experienced a stressor, a trauma, and a bereavement, and therefore had complete data on measures of PTSD, CPTSD, PGD, and AjD. To include only those participants who fulfilled the A criteria of all disorders and could thus possibly suffer from any of the four disorders, all analyses were based on responses from these participants. The mean age of this sample was 45.42 years (Mdn = 45.00, SD = 14.69, range 18-87), and 51.1% were female. Ireland is comprised of four regional Provinces and 53.1% of participants resided in Leinster (east of the country including the capital city of Dublin), 27.2% resided in Munster (south of the country), 14.4% resided in Connaught (west of the country), and 5.3% resided in Ulster (north of the country, not including Northern Ireland). Most participants were in a committed relationship (70.5%) and had children (62.9%). Secondary school completion was the highest educational attainment for 39.2% of the sample, 37.9% completed an undergraduate degree, 15.5% completed a postgraduate degree, and 7.5% did not complete secondary school. Nearly half of participants were in full-time employment (44.3%), 18.3% were in part-time employment, 29.6% were retired, homemaking, or a student, and 7.9% were unemployed.

Measures

Trauma Exposure

The *International Trauma Exposure Measure* (ITEM) [4] includes descriptions of 21 events that reflect the ICD-11's description of a traumatic event as an 'extremely threatening or horrific event'. Participants are asked to indicate if they experienced each event during three developmental periods: 0-12 years, 13-18 years, and older than 18 years. Lifetime exposure was indicated if the event occurred in any one of these periods. Participants were also asked to identify their most distressing traumatic event, if they were exposed to multiple traumatic events.

PTSD and CPTSD

The *International Trauma Questionnaire* (ITQ) [5] is an 18-item measure that respondents complete in relation to their most distressing traumatic event. Six items measure the PTSD symptoms of 'Re-experiencing in the Here and Now' (Re), 'Avoidance' (Av), and 'Sense of Current Threat' (SoT), and are answered in terms of how bothersome the symptoms have been in the past month. Six items measure the DSO symptoms of 'Affective Dysregulation' (AD), 'Negative Self-Concept' (NSC), and 'Disturbed Relationships' (DR), and are answered in terms of how respondents typically feel, think about themselves, and relate to others. The PTSD and DSO symptoms are accompanied by three items measuring functional impairment in the domains of social, occupation, and other important areas of life. All items are answered using a five-point Likert scale that ranges from 0 (*Not at all*) to 4 (*Extremely*). The internal reliability of the PTSD ($\alpha = .89$), DSO ($\alpha = .91$), and total ($\alpha = .92$) scale scores in this sample were excellent.

PGD

The *Inventory of Complicated Grief-Revised* (ICG-R) [18] first asks respondents, "At any time in your life, has someone close to you died (e.g., a partner, parent, child, friend)?" If a respondent answers '*Yes*', they are asked to indicate how long ago the death occurred (less than six months ago, 6-12 months ago, 1-5 years ago, or more than 5 years ago), and to

answer seven questions measuring PGD symptoms over the past month. There is one question measuring functional impairment associated with these symptoms. A five-point Likert scale is used for all items. We included all participants who reported any bereavement. The internal reliability of the scale scores in this sample was excellent (α = .89).

AjD

The *International Adjustment Disorder Questionnaire* (IADQ) [7] initially asks respondents to complete a psychosocial stressor checklist which includes descriptions of nine broad categories of stressful life events (e.g., 'I am currently experiencing relationship problems [e.g., break-up, separation or divorce, conflict with family or friends, intimacy problems']). Participants are then asked to answer all subsequent questions in relation to one of their identified stressors. There are three items measuring the 'Preoccupation' symptoms and three items measuring the 'Failure to Adapt' symptoms, and these items are answered in terms of how bothersome the symptoms have been in the past month. There are four additional questions to assess if these symptoms began within one month of the stressful event and if these symptoms are associated with functional impairment. All items are answered on a five-point Likert scale that ranges from 0 (*Not at all*) to 4 (*Extremely*). The internal reliability of the Preoccupation (α = .90), Failure to Adapt (α = .92), and Total Scale (α = .95) scores were excellent.

Analysis

In a symptom network, nodes represent symptoms and edges reflect pairwise relations between these symptoms, visualizing the multivariate interdependencies of symptoms. For our analysis, six PTSD symptoms, six DSO symptoms, seven PGD symptoms, and six AjD symptoms were included in the network estimation procedure. Please see supplement 1 for details regarding analysis.

Results

Descriptive statistics of the 25 symptoms are reported in Table 1.

Table 1 here

Figure 1 depicts the symptom network for the 25 symptoms. About half of all possible edges were estimated to be non-zero (47.3% of 300) and most identified associations were positive (89.4% of all non-zero edges). The strongest association found in the network emerged between the two symptoms of negative self-concept (part of the DSO cluster in CPTSD). All edges within each diagnostic category were positive and all transdiagnostic edges connecting symptoms of the three disorders PTSD, DSO, and AjD were positive. In contrast, the only negative edges in the network were estimated between symptoms of PGD and symptoms of the other three disorders. The average connections were higher within the four conditions than between; PGD symptoms showed the lowest average connections to the other three conditions.

Figure 1 here

The most central symptom in the entire network was PGD3 *(I feel as if a part of me died)*. The most central symptom for AjD was AjD5 (*Difficulty relaxing),* for PTSD was AV1 (*Internal avoidance*), for CPTSD was NSC2 (*Worthlessness*) (see Figure 2). The strongest bridge symptoms were SoT2 (*Startle response*), AjD6 (*Difficulties to achieve inner peace*), PGD5 (*Difficulty to move on with one's life*), and AjD1 (*Difficulty calming down*). The correlation between the standard deviation of the nodes with strength and expected influence was low ($r < .26$), ruling out a possible bias [19]. The mean predictability (illustrated by the percentage of shaded area in the pie around the nodes in Figure 1) of the full network was 0.61, indicating that, on average, 61% of the variation of each symptom could be explained by its neighbouring symptoms. The nodes with the highest predictability were NSC1 (*Feeling like a failure*) and NSC2 (*Worthlessness*) and the node with the lowest predictability was AD1 (*Difficulty calming down*).

243 Figure 2 here

244 The community detection procedure found the same solution in each of the 10,000 bootstrap
245 iterations and this solution was identical to the disorder categories, placing each symptom in
246 one cluster with all other symptoms of the respective condition. The stability analyses of the
247 network supported the accuracy of the estimated network (see Supplementary materials) and
248 all CS-coefficients were > .59.

249 **Discussion**

250 The introduction of the disorders specifically associated with stress in ICD-11 provides an
251 opportunity to explore and respond to the needs of people with distinct patterns of symptoms
252 as a result of a defined stressor. There has been evidence to suggest that different stressors
253 can produce a range of different disorders specifically associated with stress or different
254 patterns of prominent symptoms within individual conditions [12]. This study set out to test
255 the distinctiveness of the four main ICD-11 disorders associated with stress using a network
256 psychometric approach in a representative sample of adults from the general population.
257 Consistent with the taxonomic structure of the ICD-11, our results showed that the specific
258 symptoms of PTSD, CPTSD, PGD, and AjD clustered together very strongly, and more
259 strongly than with symptoms of the other disorders. Interventions addressing stress-
260 associated disorders should thus be based on profound diagnostic assessment to ensure close
261 fit between symptoms and treatment. The majority (61%) of the variation in each symptom
262 could be explained by its neighbouring symptoms. As expected, most of the connections were
263 positive, however, and notably, several PGD symptoms were negatively associated with the
264 PTSD, CPTSD, and AjD symptoms. The strongest trans-diagnostically connecting symptom
265 was “startle response”, putting the reaction to an inner sense of ongoing exposure to stressors
266 or reminders of a stressor at the heart of stress-associated comorbidity.

The large amount of explained variability within the network substantiates the common ground on which stress-related disorders develop in individuals. This is the first network analytical study including all ICD-11 stress-associated disorders, however, the symptom-covariation is similar to previous results in PTSD and DSO [17] and PGD networks [18]. Despite the strong overall connectivity, we found clear communities of symptoms representing the four diagnostic categories, advocating the distinction and network psychometric validity of the specific disorders within the umbrella group. While symptoms were connected across all diagnostic categories, they clustered together in communities only with other symptoms from their respective disorder. We repeated this community analysis 10,000 times to ensure robust results and found the same solution every single time. Importantly, our findings also illustrate that mental disorders are not independent entities. Psychopathological conditions may reinforce each other on a symptom level and across disorders. Interestingly and in contrast to our expectations, some of the associations between PGD symptoms and the other conditions were negative. Taking a closer look at these associations, they appear plausible. For example, "Internal avoidance" was negatively associated with "Preoccupation with the deceased"; constantly being preoccupied with the loss of a lost loved one could be described as the opposite end of a dimension from preoccupation to internal avoidance. PGD is characterized theoretically as involving yearning for the deceased [22], which is supported by evidence in PGD of distinct neural processes in reward processing networks [23], as well behavioural evidence of approach tendencies [24-25]. This evidence of disturbed approach or reward processes in PGD is consistent with the observed network findings in this study, which suggest that the association of PGD symptoms may function somewhat distinctly relative to the other stressor-related disorders. However, these negative associations were small, and the stability analyses indicated that their presence should be interpreted with care.

The symptom with the strongest connections across categories was “Startle response”. This symptom showed a particularly strong connection to the DSO symptom “Affective hyporegulation”, which can be explained by a common deficit in regulating inner experiences. “Startle response” might be a sign of ongoing, potentially subconscious, occupation with the stressors including an ongoing physiological stress reaction that manifests in strong reactions to minor triggers. Responding, psychologically and (psycho)somatically, to the triggering events is common across all stress-related disorders and could explain the central position of “Startle response” in connecting disorders. The second strongest connection of symptoms across disorders was between the AjD symptom “Difficulties to adapt” and the PGD symptom “Difficulty moving on with life”, reflecting similar problems of adaptation after burdensome life-events. Overall, our findings suggest that the large amount of explained variability within the network and the strong communities of different disorders support the umbrella category of disorders specifically associated with stress that was introduced in ICD-11.

Further work is required to explore the unique features of these conditions and their applicability in different cultural contexts. ICD-11 has been developed with clinical utility and global applicability in mind [26]also including middle to low income countries and therefore it is important to explore the distinctiveness of these conditions in various cultural and socioeconomic contexts. Mental health professionals who care for people who have experienced a range of stressors and traumatic life events are encouraged to pay attention to the type of stressor and the phenomenology of symptoms to make an ICD-11 disorder specifically associated with stress diagnosis. There is now greater specificity to PTSD and CPTSD in ICD-11 for those exposed to traumatic life events whereas there is the alternative and better defined diagnosis of AjD for those exposed to stress. The introduction of prolonged grief disorder in ICD-11 is the result of a perceived clinical need while recognising

317 that people with this pattern of symptoms might require specialised care [27], which is
318 different from what is offered to those with PTSD or CPTSD.
319 Although caution should be exercised in the interpretation of the concept of centrality in
320 network analysis [28], central symptoms may provide guidance in the selection of therapeutic
321 targets in order to improve treatment response rapidity. These results have important
322 implications for the treatment of specific conditions. As an example, Karatzias and Cloitre
323 propose that through the use of the flexible delivery of modular treatment components, the
324 symptoms of CPTSD can be targeted and organized in therapy according to the severity or
325 prominence of a symptom cluster alongside a patient's preferences about which problems are
326 most troublesome [29]. The analysis reported in this paper has identified individual central
327 symptoms for each of the conditions. "Feeling one has lost a part of one's self" was the most
328 central prolonged grief disorder symptom, contrasting previous results (i.e. intense feelings of
329 sorrow and inability to experience joy or satisfaction [21]). Nevertheless, it should also be
330 noted that previous studies in the area focused on the symptom networks of one disorder
331 whereas the present on four different conditions. For ICD-11 adjustment disorder,
332 "Difficulties to relax" was the most central symptom and no previous study has been
333 published on the network structure of the revised adjustment disorder as of yet. Indeed,
334 treatments for adjustment disorder include modules focusing on relaxation [30]. "Internal
335 avoidance", the most central PTSD symptom in our network, is considered a core aspect of
336 PTSD by theoretical models [31], maintaining other symptoms. Finally, "worthlessness*"* is
337 repeatedly identified as most central symptom in Complex PTSD networks in relevant studies
338 [11,20], supporting its clinical importance as a problem that an effective therapy should
339 address. Prioritising these symptoms in treatment may lead to faster recovery; however, the
340 centrality hypothesis has received conflicting empirical support so far [32] and requires
341 further investigation.

Our study had a number of limitations. First, we have used a community sample and these results may not generalize to treatment-seeking, clinical samples. Second, the cross-sectional nature of the sample does not allow for any causal inferences to be drawn, although it has been argued that cross-sectional networks are a useful first step for the initial testing of theories [33]. Third, we used self-report questionnaires for assessment and clinician administered interviews might have provided more valid data. Fourth, we did not exclude participants who were bereaved within the last six months (n = 42), which is in contrast to ICD-11's diagnostic criteria. However, in a sensitivity analysis not reported here, no substantive change occurred when excluding these participants. Finally, we have not explored associations between the symptom clusters of these disorders and other common co-morbid conditions such as depression and general anxiety. Notwithstanding its limitations this is the first study to explore the distinctiveness and network psychometric validity of the ICD-11 conditions specifically associated with stress. Our results suggest that these conditions can be reliably used by health care professionals in clinical practice to diagnose people who have been exposed to various stressors to plan their treatment and care. Although there are distinct pathways from stressors to unique disorders associated with stress, at the same time our study identified key symptoms within and between these disorders that may provide insight for more targeted, effective interventions for those in need.

Statements

Statement of ethic: This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the Social Research Ethics Committee at Maynooth University, approval number SRESC-2020-2402202.

Consent to participate statement: Written informed consent was obtained from participants prior to their participation

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Author Contributions:

Thanos Karatzias - Conceptualisation, writing original draft, Matthias Knefel - Data analysis, writing, Andreas Maercker - Writing review – editing, Marylene Cloitre - Writing review – editing, Geoffrey Reed - Writing review – editing, Richard Bryant - Writing review – editing, Menachem Ben-Ezra - Writing review – editing, Evaldas Kazlauskas - Writing review – editing, Sally Jowett - Writing review – editing, Mark Shevlin - Data curation, methodology Philip Hyland - Data curation, methodology

Declaration of interests: None to declare.

Data availability statement: All data used this work will be available upon request following a signed data access agreement following publication.

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Figure 1: *Symptom network of ICD-11 disorders specifically associated with stress*.

Figure 2: *Centrality estimates*